REMARKS

1. Status of the Claims

Claims 1, 2, 4 through 15 and 72 through 83 are pending in the application. Claims 16 through 71 are cancelled. Claim 15 stands rejected under 35 USC 112, first paragraph. Claims 1, 2, 4 through 8 and 72 through 81 stand rejected under 35 USC 102(a). Claims 1 and 2 stand rejected under 35 USC 102(b). Claim 1, 2, 4 through 15 and 72 through 83 stand rejected under 35 USC 103(a).

2. The rejection under 35 USC 112, first paragraph, must be withdrawn

The examiner maintained rejection of claim 15 under 35 USC 112, first paragraph, for reasons of record in an Office Action mailed July 29, 2003, asserting that "no arguments were presented addressing the scope of enablement rejection of the claims" [Office Action, p. 2]. Briefly, the examiner asserted that the claimed method is enabled for inhibiting hormone sensitive lipase (hsl) *in vitro*, but "the examples provided in the instant application are not representative of inhibiting the target gene hlp of SEQ ID NO: 3 in an organism comprising the administration, by any means, of the antisense compound.[Office Action, pp. 2-3]. The applicants respectfully traverse the rejection.

The application expressly discloses not only that *in vivo* administration of claimed compounds in a obese mouse model inhibits liver mRNA expression levels of hsl [Example 20], but that administration of claimed compounds reduces blood glucose levels [Example 19], reduces liver weight without affecting fat weight [Example 21], decreases serum insulin levels [Example 22], decreases liver enzyme AST and ALT levels [Example 23], and decreases serum cholesterol and triglyceride levels [Example 24], all as shown in the same mouse model. In a mouse model for hyperlipidemia, administration of claimed compounds reduces liver hsl mRNA expression [Example 28] and serum cholesterol and serum triglyceride levels [Example 29]. In two distinct models, therefore, the application teaches that compounds of the invention can be administered to an animal resulting in inhibition of hsl mRNA expression, and that this administration provides specific biological responses.

In view of the extent of this disclosure, the applicants submit that the rejection of claim 15 under 35 USC 112, first paragraph, must be withdrawn.

3. The rejections under 35 USC 102 must be withdrawn

A. Claims 1, 2, 4-8, 11-15, and 72-81

Claims 1, 2, 4-8, 11-15, and 72-81 were also rejected under 35 USC 102(a) as being directed to subject matter allegedly anticipated by the disclosure of Mitchell for reason set out in the Office Action mailed July 29, 2003. The examiner asserted that Mitchell discloses antisense compounds between 8 and 50 nucleobases that specifically target and inhibit the expression of SEQ ID NO. 3 *in vitro*. It was the examiner position that, absent evidence to the contrary, antisense designed according to the teaching of Mitchell would inherently possess the same functional activity as the applicant's claimed antisense. The applicants respectfully traverse.

A proper anticipatory reference under section 102 must disclose every element of the invention as claimed. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.") In this case, however, the examiner asserts that the cited reference teaches each element but fails to point out where in the reference each element is disclosed.

For example, the examiner asserts that Mitchell discloses antisense oligonucleotides between 5 and 50 bases in length but does not indicate where. Mitchell, at page 4, does refer to antisense having five or more contiguous nucleic acid resides substantially complimentary to a contiguous portion of a nucleic acid encoding hsl, and at page 8 further mentions antisense having from about 5 to about 100 nucleotide units, but Mitchell does not disclose compounds 8 to 50 nucleobases in length. This particular example is problematic to the examiner's position in view of the anticipation analysis required with respect to a recited subrange in view of a prior art disclosure of a broader range.

According to MPEP 2131.03,

> When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are

> directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims.

Here, Mitchell lacks disclosure of the class of compounds having the specifically recited length of 8 to 50 nucleobases, and fails to disclose a specific example of a compound of this range length. In fact, Mitchell fails to disclose any specific antisense compounds, much less any that actually inhibit expression of hsl to any degree in any cell type. Accordingly, Mitchell does not disclose an antisense compound that can inhibit hsl expression by at least 5% in HepG2 cells. Because Mitchell fails to disclose even this aspect of the claimed invention with any degree of specificity, the reference cannot anticipate the invention and the rejection must be withdrawn.

B. Claims 1 and 2

Claims 1 and 2 were also rejected under 35 USC 102(b) as being directed to subject matter assertedly anticipated by the disclosure of Holst for reason set out in the July 29, 2003 Office Action. The examiner maintained that Holt discloses antisense compounds between 8 and 50 nucleobases that specifically target and inhibit the expression of SEQ ID NO. 3 *in vitro*. It was the examiner position here again that, absent evidence to the contrary, antisense deigned according to the teaching of Holst would inherently possess the same functional activity as the applicant's claimed antisense. The applicants respectfully traverse the rejection for essentially the same reasons as set out above.

The examiner relies on the disclosure in Holst of a single antisense PCR primer to assertedly anticipate the claimed invention, however, nothing in Holst suggests that this primer can be used to inhibit expression of hsl, much less that it would actually inhibit hsl expression by 5% in any cell type. Despite this deficiency in the Holst disclosure, applicants have amended claim 1 to remove from the scope of the invention the region in an hsl-encoding nucleotide acid to which the Holst primer may hybridize, thereby obviating the rejection.

C. Claims 1 and 2

Claims 1 and 2 were also rejected under 35 USC 102(b) as being directed to subject matter assertedly anticipated by the disclosure of Langin for reason set out in the July 29, 2003 Office Action. The examiner maintained that Langin discloses antisense compounds between 8 and 50 nucleobases that specifically target and inhibit the expression of SEQ ID NO. 3 *in vitro*. It was the examiner position here again that, absent evidence to the contrary, antisense deigned according to the teaching of Langin would inherently possess the same functional activity as the applicant's claimed antisense.

Similar to the rejection based on the disclosure of Holst, the examiner relies on disclosure in Langin of "an end-labeled 21-mer antisense oligonucleotide that maps to 130 nt downstream from nt +1" used in primer extension to assert anticipation of the claimed invention. This disclosure in Langin differs from Holst in that the sequence of the 21-mer is not disclosed and the mere statement that this primer "was hybridized" to RNA in the primer extension assay says nothing about its sequence or its capacity to inhibit hsl expression to any degree in any cell type.

It is well known in the art that the ability of a single stranded nucleic acid to hybridize to any other single stranded nucleic acid is determined by a number of factors, including salt conditions under which hybridization is attempted. For example, in an extreme instance, under sufficiently high salt concentration (which neutralizes repulsive positive charge of the phosphate backbone of the two nucleic acids), it is possible to "force" almost any two single stranded nucleic acids to hybridize regardless of sequence complimentarity. Given that Langin fails to disclose the conditions under which the primer extension experiment was carried out, we known nothing about (i) the sequence of this 21-mer, (ii) whether this 21-mer will hybridize to an hsl-encoding nucleic acid under physiological conditions, (iii) assuming it does hybridize under physiological conditions, whether the 21-mer will inhibit hsl expression at all, or (iv) whether the 21-mer will inihibt hsl expression to any degree in HepG2 cells. Accordingly, the applicants submit that the lack of specificity in the disclosure of Langin must disqualify its teaching as anticipatory art and the rejection of claims over this disclosure must be withdrawn.

4. <u>The rejections under 35 USC 103 must be withdrawn</u>

Claims 1, 2, 4-15 and 72-83 were rejected under 35 USC 103(a) as being directed to subject matter assertedly rendered obvious in view of the disclosures of Mitchell, Holst and Langin further in view of the disclosures of Milner and Baracchini. Mitchell, Holst and Langin were cited for reasons stated above with respect to rejections under 102. Milner was cited for disclosing a method for "designing antisense compounds for targeting regions essentially blanketing a target gene of known sequence, then testing for inhibition of expression of that target gene. [Office Action, p. 5] Baracchini was cited for disclosing "the general applicability of modifications incorporated into antisense to enhance their stability, target binding and cellular uptake." [Office Action, p. 6] The examiner concluded that combination of these disclosures provides "general knowledge and motivation that render the claimed invention obvious." [Office Action, p. 6] The applicants respectfully traverse.

First, the applicants submit that the disclosures of Holst and Langin are non-analogous art and immaterial to any assertion of obviousness of the claimed invention.. MPEP 2141.01(a) states,

> "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). See also In re Deminski, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986); In re Clay, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) ("A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); and Wang Laboratories Inc. v. Toshiba Corp., 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993).

If the "particular problem with which the inventor was concerned" is understood to be inhibition of hsl expression using antisense, and the sequence of the nucleic acid encoding hsl was known, the applicant submits that the worker of ordinary skill would have no reason to consider the disclosures of either Holst or Langin which are unrelated to inhibiting hsl expression. Both references relate to cloning and nothing more.

Mitchell, as discussed above provides a broad generic disclosure of how to make antisense compounds, but discloses no specific compounds and fails to disclose with

any degree of specificity the invention as presently claimed. Whether any antisense compounds having the physical and functional properties of the claimed compounds could be obtained using the disclosure of Mitchell is unknown because Mitchell provides no working examples, and as a result, the disclosure of Mitchell is nothing more than an invitation to produce useful antisense.

Milner discloses use of arrays of oligonucleotides to identify antisense compounds that hybridize to a portion of a polynucleotide encoding rabbit β-globin and which inhibit *in vitro* translation of the encoded protein. Close examination of the disclosure, however, indicates that the procedure described for a fragment of a polynucleotide encoding rabbit globin was of limited success, and this "success" did not produce an antisense compound having all of the recited limitations of the claimed compounds.

Using an array of 1938 oligonucleotides (ONs) from 1-17 bases in length, Milner first sought to identify those which would hybridize to a 122 base fragment of rabbit β-globin mRNA. [Abstract, p. 537] Each of the ONs utilized was complementary to a portion of the 122 base target region. [Abstract, p. 537] Of the 1938 ONs tested, only one sequence gave "high" duplex yield, a 15mer corresponding the bases 46-60 in the 122 base target, and this 15 base sequence was also found in two 16mers and three 17mers. [p. 537, second column, first paragraph] These six ONs giving "high" duplex yield, therefore, represent less than 0.5% of the 1938 ONs tested. While other ONs showed weak hybridization [p. 537, second column, first paragraph], their value for inhibiting β-globin expression is unknown since only one of the ONs showing high level of duplex formation, BG1, a 17mer containing a region complementary to bases 46-60 in the target, was tested for its capacity to inhibit protein expression. [p. 538, first column, first paragraph] Others tested included a previously identified positive control BG2 and a negative control BG3. [p. 538, first column, first paragraph] In the *in vitro* translation assay, results showed that at 10 μM all three ONs inhibited both α-globin and β-globin synthesis, and at 1 μM, BG1 and BG2 (but not negative control BG3) inhibited β-globin but not α-globin synthesis. [p. 539, first column, first complete paragraph]

From the results, and contrary to any assertion by Milner, the *in vitro* translation results fail to demonstrate that the inhibitory action of the one "successful" oligonucleotide was through *specific* hybridization as recited in claim 1 and defined in the specification. The specification at page 9, line 31, to page 10, line 6, teaches,

> An antisense compound is *specifically hybridizable* when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, *and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense* compound *to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.* [Emphasis added.]

Results from Milner's *in vitro* assay, however, showed that the single oligonucleotide identified in the array experiment (BG1) was capable of inhibiting both α-globin and β-globin synthesis in the *in vitro* translation assay, indicating that this oligonucleotide lacks the specificity required in the rejected claims and as defined in the specification. This same lack of specific hybridization was also observed with the positive control BG2 oligonucleotide. While Milner asserts specificity could be induced at lower concentrations, the fact remains that the BG1 oligonucleotide is capable of non-specific hybridization.

Moreover, assuming *arguendo* that Milner actually identified a compound with the requisite specificity of hybridization, the "success" rate for the disclosed method was one out of the 1938 oligonucleotides tested, or about 0.05%. Considering the extremely low level of demonstrated "success" for inhibiting β-globin expression, the applicants submit that these results fail to provide the skilled worker with the reasonable expectation of success for identifying antisense compounds that would inhibit other target polynucleotides.

The combination of these disclosures therefore fails to demonstrate that any antisense compound can be prepared that would specifically inhibit hsl expression either in cell culture to the degree explicitly recited or in any other environment. Because the combination cannot render obvious the subject matter of any pending independent claim, it is axiomatic that the same combination cannot render obvious any claims depending therefrom. *See, e.g., In re Fine*, 837 F.2d 1071. The applicants therefore submit that the rejection of claims under section 103 must be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

By _____

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